

Applicants: MEIJER, Christophorus et al.  
U.S. Serial No.: Not yet known  
Based on Int'l. Serial No.: PCT/NL2004/000118  
Page 2

**Amendments to the Claims:**

Please amend the claims as follows:

1. (Currently Amended) A method of detecting an HPV-induced invasive cancer or precursor lesion thereof associated with tumor suppressor lung cancer 1 (TSLC1) in a subject in need thereof, ~~said~~ the method comprising contacting a cell component of a test cell of the subject with a reagent that detects the level of the cell component in the test cell and determining a modification in the level of the cell component in the test cell as compared with a comparable healthy cell, wherein the cell component indicates the level of TSLC1 in the cell and wherein a decrease in the level of TSLC1 indicates the presence of an HPV-induced invasive cancer or precursor lesion thereof.
2. (Currently Amended) ~~Method~~ A method according to claim 1, wherein ~~said~~ the HPV-induced invasive cancer or precursor lesion thereof is invasive cervical cancer or a premalignant cervical lesion with invasive potential.
3. (Currently Amended) ~~Method~~ A method according to claim 1 [or 2], wherein ~~said~~ the HPV-induced invasive cancer is a high-risk HPV-induced invasive cancer.
4. (Currently Amended) ~~Method~~ A method according to ~~any one of the~~

~~preceding claims~~ claim 3, wherein the cell component is a nucleic acid associated with production of TSLC1 polypeptide, [and] the reagent targets the nucleic acid in the test cell, ~~said and the~~ nucleic acid preferably encoding encodes the TSLC1 and regulatory regions.

5. (Currently Amended) ~~Method~~ A method according to ~~claims~~ claim 4, wherein the nucleic acid is RNA, ~~preferably mRNA.~~
6. (Currently Amended) ~~Method~~ A method according to ~~any one of the preceding claims~~ claim 4, wherein the reagent is a restriction endonuclease[,], ~~preferably a methylation sensitive restriction endonuclease.~~
7. (Currently Amended) ~~Method~~ A method according to claim 5, wherein the reagent is a nucleic acid probe or primer that binds to the nucleic acid, ~~said nucleic acid probe or primer preferably~~ having a detectable label.
8. (Currently Amended) ~~Method~~ A method according to claim 7, wherein the nucleic acid probe has [a] one of the following nucleotide sequences: ~~selected from the group consisting of:~~
  - a) a polynucleotide sequence capable of hybridizing under stringent conditions to the 5' regulatory region or the coding region of the

~~TSLC1~~ TSLC1 sequence as set forth in Figure 1;

- b) a polynucleotide sequence having at least 70% identity to the polynucleotide of a);
- c) a polynucleotide sequence complementary to the polynucleotide sequence of a); [and] or
- d) a polynucleotide sequence comprising at least 15 bases of a nucleotide polynucleotide sequence of a) or b).

- 9. (Currently Amended) Method A method according to claim 8 ~~any one of the claims 1-4~~, wherein the cell component is a polypeptide and the reagent targets the polypeptide in the test cell, ~~said~~ and wherein the polypeptide ~~preferably being is~~ TSLC1 and ~~said the~~ reagent ~~preferably being is~~ an anti-TSLC1 antibody.
- 10. (Currently Amended) Method A method according to claim 2 ~~any one of the claims 1-5~~, wherein ~~said the~~ method of detecting evaluates the methylation status of the ~~TSLC1~~ TSLC1 promoter.
- 11. (Currently Amended) A method of detecting an HPV-induced invasive cancer or a precursor lesion thereof associated with tumor suppressor lung cancer 1 (TSLC1) in a subject ~~in need thereof~~, ~~said the~~ method comprising contacting a target cellular component of a test cell with a

reagent that detects TSLC1 and detecting a reduction in the TSLC1 as compared to that of a comparable normal cell, ~~preferably in said detection~~ an increased methylation of the ~~TSLC1~~ TSLC1 promoter in the test cell ~~and/or,~~ a reduced production of TSLC1 in the test cell as compared to the comparable normal cell is determined, or both.

12. (Currently Amended) ~~Method~~ A method according to claim 11, wherein the target cellular component is a nucleic acid.
13. (Currently Amended) ~~Method~~ A method according to claim 12, wherein the nucleic acid is ~~RNA,~~ preferably mRNA.
14. (Currently Amended) ~~Method~~ A method according to claim 11, wherein the target cellular component is a protein.
15. (Currently Amended) ~~Method~~ A method according to claim ~~12 or 13~~ 11, wherein the reagent is a nucleic acid probe or primer that binds to TSLC1.
16. (Currently Amended) ~~Method~~ A method according to claim 14, wherein the reagent is an anti-TSLC1 antibody.
17. (Currently Amended) ~~Method~~ A method according to ~~any one of the claims~~

44-46, wherein subject has loss of heterozygosity at chromosome 11q23.

18. (Currently Amended) A method of treating HPV-induced invasive cancers and their precursor lesions associated with modification of TSLC1 production in cells in a subject ~~in need thereof~~ afflicted with such a cancer or lesion, ~~the said method comprising contacting cells of the subject said cells of a patient suffering from said cancer with a therapeutically effective amount of a reagent that increases TSLC1 level in said~~ the cells of the subject.
19. (Currently Amended) ~~Method~~ A method according to claim 18, wherein the reagent includes ~~is a polynucleotide sequence comprising a~~ TSLC1 sense polynucleotide sequence, ~~preferably said polynucleotide is the native, unmethylated TSLC1 sense sequence.~~
20. (Currently Amended) ~~Method~~ A method according to claim 19, wherein a nonmethylatable analog is substituted for cytidine within the TSLC1 sense sequence, ~~said~~ and wherein the nonmethylatable analog ~~preferably being~~ is 5-azacytadine.
21. (Currently Amended) ~~Method~~ A method according to claim ~~19~~ or 20, wherein ~~said~~ the polynucleotide sequence is contained in an expression

vector, ~~said and the~~ expression vector preferably ~~being~~ is a plasmid, a viral particle or a phage.

22. (Currently Amended) ~~Use of a~~ A molecular diagnostic marker for detection of progression to invasiveness of HPV-induced premalignant lesions associated with tumor suppressor lung cancer 1 (TSLC1) and for detection of future metastatic potential of HPV-induced premalignant lesions and carcinomas associated with tumor suppressor lung cancer 1 (TSLC1), wherein ~~said the~~ marker indicates ~~TSLC1~~ TSLC1 promoter methylation, ~~and/or~~ expression of mRNA associated with production of TSLC1 polypeptide[.], or both.
23. (Currently Amended) ~~Kit of parts~~ A kit for use in a method of detecting HPV-induced invasive cancers and their precursor associated with tumor suppressor lung cancer 1 (TSLC1) in test cells of a subject, ~~said the~~ kit comprising means to collect test cells and ~~means for the detection of~~ TSLC1 promoter methylation or TSLC1 expression the molecular diagnostic marker of claim 22.
24. (Currently Amended) ~~Kit of parts~~ A kit for use in a method of detecting HPV-induced invasive cancers and their precursor lesions associated with tumor suppressor lung cancer 1 (TSLC1) in test cells of a subject,

said ~~the~~ kit comprising primers and probes capable of ~~hybridising~~  
hybridizing to ~~TSLC1~~ TSLC1 nucleotide sequence of Figure 1, TSLC1  
antibodies, or methylation sensitive restriction enzymes recognizing the  
sequence as described in Figure 1.

25. (Currently Amended) ~~Kit of parts~~ A kit according to claim ~~23 or 24~~23,  
wherein the test cells are cervical cells.
26. (New) A method according to claim 5, wherein the RNA is mRNA.
27. (New) A method according to claim 6, wherein the reagent is a methylation  
sensitive restriction endonuclease.
28. (New) A method according to claim 19, wherein the polynucleotide is the  
native, unmethylated TSLC1 sense sequence.